REPRODUCTIVE PERFORMANCE OF MICE SELECTED FOR REPRODUCTIVE LONGEVITY

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INTRODUCTION

Poor reproductive performance is one of the major causes for culling, which leads to a decrease in profitability in various livestock (Durr *et al.,* 1997 ; Kulak *et al.,* 1997 ; Tanida *et al.,* 1988). Improving reproductive longevity (RL) offers one of the greatest opportunities for increasing productive efficiency and economic return in the livestock industry. Despite its obvious economic importance, it is difficult to improve RL through conventional breeding methods because of the low heritability of this trait (Tanida *et al*., 1988 ; Boldman *et al.,* 1992 ; VanRaden and Klaaskate, 1993) and the long time needed to obtain information on RL in livestock. These limitations make RL an ideal candidate trait for the use of DNA markers (Lande and Thompson, 1990). Developing DNA markers for RL is, however, a time-consuming and prohibitively expensive task in long-lived livestock species. A logical strategy would involve identification of putative candidate genes in a mammalian model with a short generation interval, such as mice, and later validating them in livestock. The availability of information on the mouse genome and laboratory procedures to facilitate high-throughput scanning of the entire mouse genome are no longer bottlenecks in the process of gene discovery and elucidation of the genetic control of a complex trait such as RL. Instead, having access to a suitable population with contrasting phenotypes is the limiting factor. Here we describe reproductive performance of a mouse colony that has been selected for RL for 24 generations, and is a valuable mammalian model in searching for genes that modulate this complex trait in mammals.

MATERIALS AND METHODS

Establishment of the colony. The original mouse population, which was established in 1965, was a cross between two strains : P and Q. The P strain was a cross between four inbred lines (C3H/HeJ, C57BL/6J, CBA/J, SWR/J) and the Q strain, which was established by Falconer in 1960, had a substantial heterogeneous background (Garnett and Falconer, 1975). Prior to the implementation of the selection program for RL, both the P and Q stocks were maintained by random mating for 23 generations to achieve linkage equilibrium. Two lines from each of the P and Q strains were then established, each with 92 pairs of breeders. One line derived from each of the P and Q stocks was selected for nursing ability of the mother, and the other for body weight of progeny at 42 d of age. After 21 generations of selection, these four lines were crossed, and the synthetic stock was maintained by random mating for 12 generations to allow it to approach linkage equilibrium (Nagai *et al.,* 1995). The contribution of so many lines to

this colony ensured that many alleles were segregating in the base population. Consequently, this is the most heterogeneous mouse model in the world which has been selected for RL. The four inbred lines and three of the lines that contributed to the Q strain (SM/J, LG/J, JU) are currently maintained at the Jackson Laboratories, Bar Harbor, Maine, USA. Having access to DNA, phenotypic and genetic information on these lines makes it possible to trace chromosomal segments of animals of the current generations back to the base population, and would facilitate interpretation of genetic changes that had taken place in this colony as a result of long-term selection for RL.

Selection scheme. One control (C1) and two selected lines, with (SA1) and without (SU1) standardizing litter size to 8, were established in 1982 and have been continuously selected for RL since then (Nagai *et al.,* 1995). Replications from each of the control and selected lines were established (C2, SA2, SU2) in 1993. In each of the selected lines, one male and one female were caged at about eight weeks of age, and each pair was maintained in the same cage continuously until the next generation was established, using progeny from parity six and higher. In the control lines, progenies from the first parity were used as breeders. Control and selected lines were maintained with 42 and 30 breeding pairs, respectively, avoiding full-sib mating (Nagai *et al.,* 1995).

Performance evaluation at generation 24. Breeder males and females from generation 24 of the selected lines SA1 (31 pairs), SU1 (28 pairs) and generation 69 of the C1 line, corresponding to generation 24 of the selected lines (42 pairs), were caged. Animals were maintained until the end of their natural life. Pairing date, parturition date, litter size at birth (dead or alive) and at weaning (21 d), sex of pups at weaning, and date of pup and adult mortality were recorded. RL was calculated as the number of days between pairing and the last parity, defined as when a female did not conceive for at least 60 days. In a few instances, trace of blood was observed, which could be the sign of pup mutilation, and was considered as a parity.

RESULTS AND DISCUSSION

The number of pairs that completed the test, i.e. both male and female were alive at least 60 days after the last parturition, was 22 (71.0 %), 15 (53.5 %) and 35 (83.3 %) for SA1, SU1 and C1 lines, respectively. Death or termination of females as a result of severe pregnancy complications or prolapse, particularly at later parities, were the main reasons for failure of a pair to complete the test (more than 77 % of the cases). A higher number (10) of females in the unstandardized line (SU1) encountered such complications, which resulted in this line to have the lowest proportion of pairs completing the test. The high proportion of pairs that completed the test in the C1 line was the result of a shorter reproductive life of mice in this line and the fact that most of the complications in selected lines were observed at older ages.

The average number of days from mating to the last parturition (RL) when all pairs were considered was 321d in SA1 and 278 d in SU1, showing 86 % and 61 % improvement for RL in the SA1 and SU1, respectively, compared with the C1 line (173 d, table 1). RL for those pairs that completed the test was 339, 333 and 191days for the SA1, SU1 and C1, respectively, showing 77.4 % and 74.3 % improvement. Average number of parities during lifetime using

data on all original pairs were 5.3, 10.6 and 9.7 for C1, SA1 and SU1, respectively, indicating 100 % and 83 % improvement for SA1 and SU1, respectively, over the C1 line (table 1). The estimates for those animals that completed the test were 5.9, 11.0 and 11.2 for C1, SA1 and SU1, respectively, showing 86.4 % and 89.8 % improvement. The distribution of the number of parities during lifetime (figure 1) shows that the number of pairs that stoped reproducing steadily declined in the C1, while high proportions of mice in both selected lines continued reproducing. More than 50 % of pairs in SA1 and SU1 had 12 parities, which was the largest number in the C1 line.

Table 1. Means (" standard errors) for reproductive longevity (RL) and the number of parities during lifetime in generation 24[A] in selected and control lines[B]

Line	All pairs		Pairs completing the test	
	RL, d	No. of parities	RL, d	No. of parities
SA1 (Selected, standardized)	321"22a	10.6"0.7a	339"23a	11.0"0.7a
SU1 (Selected, unstandardized)	278"23a	9.7"0.7a	333"27a	11.2"0.9a
C1 (control, unstandardized)	173"19b	5.3"0.6b	191"18b	5.9"0.6b

[A]-Generation 69 for C1.
[B]-Means followed by different letters are different at P < 0.01

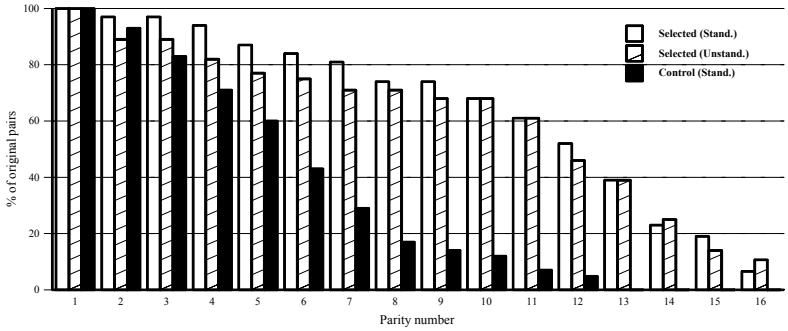

Figure 1. Distribution of number of parities during lifetime

Reproductive performance of the three lines at generations 12 and 16 is reported by Nagai *et al.* (1995). RL of SA1, SU1and C1 lines in generation 12 was 236, 265 and 159, respectively, showing 48 % and 67 % improvement. The corresponding values at generation 16 was 241, 243 and 135, indicating 78.5 % and 80 % improvement in RL for SA1 and SU1, respectively. The number of parturitions during lifetime in the C1 line has stayed unchanged in generations 12 (5.3), 16 (4.9) and 24, while the SA1 line showed a steady improvement from 8.63 in generation 12 to 8.84 in generation 16 and 10.6 in generation 24 (61.6 %, 80.4 % and 100 % improvement over the C1 line). The corresponding values for the SU1 line were 79.9 %, 93.0 % and 83.0 %. These data may suggest that while SA1 is still responding to selection, the SU1 has possibly reached a plateau for RL and the number of parities during lifetime. It may be

hypothesized that the difference between the two selected lines is the result of a higher reproductive stress on female mice in the un-adjusted SU1 line. The small generation to generation fluctuations in C1may suggest that the size of the control line was sufficient to make genetic drift a minor force in changing the genetic constitution of the lines. This observation is supported by molecular data where the SA1, SU1 and C1 lines had a comparable allele frequency distribution at a polymorphic site with their replicates (SA2, SU2, C2, Otieno *et al.,* 2001).

CONCLUSION

The significant improvement in reproductive life of the selected lines suggest that this trait can be improved by selective breeding in mammals, and that this colony is a valuable resource for finding genes that modulate reproductive longevity in livestock species.

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